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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,933	02/10/2004	Bo Hansen	58614 (71432)	2102

21874 7590 01/23/2008
EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
01/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,933	HANSEN ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-9,14-16,47-50,53,54,91 and 93-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-9,14-16,47-50,53,54,91 and 93-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 30, 2007 has been entered.

Status of Claims

Currently, claims 2, 4-9, 14-16, 47-50, 53-54, 91, and 93-105 are pending and under examination on the merits.

Response to Arguments

Applicant's arguments with respect to claims 2, 4-9, 14-16, 47-50, 53-54, 91, and 93-105 have been considered but are moot in view of the new ground(s) of rejection. See below.

Claim Objections

Claim 91 is objected to because of the following informalities: It contains two periods. Appropriate correction is required.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/446,374, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. In the instant case, the independent claim, claim 91 specifically recites a compound consisting of a total of 12-50 nucleotides and/or nucleotide analogues. It is found that the disclosure of 60/446,374 provides adequate support only for a compound comprising from about 8 to about 60, but does not provide adequate support for the claimed compound "consisting of a total of 12-50 nucleotides".

Further, claims 101-102 and 105 are drawn to compounds comprising an oligonucleotide sequence having a particular set of chemical modifications. Although the disclosure of 60/446,374 provides adequate support for SEQ ID NO:8 having "CAAGgaatatcaCGTT" or "CAAGgaatatcacGTt" wherein the capitalized letters indicate β-D-oxy-LNA and wherein all

nucleotides contain phosphorothioate linkages except the most 3' end nucleotide, it does not provide adequate description/support for the specific structures of compounds of claims 101-105 that comprise a mix of phosphorothioate and phosphate linkages. Further, the disclosure of 60/446,374 does not provide adequate support for the compound of claim 97, which "consists of a total of 12-20 nucleotides and/or nucleotide analogues". Page 18 of 60/446,374 instead discloses, "Particularly preferred compounds are antisense oligonucleotides comprising from about 12 to about 30 nucleobases and most preferably are antisense compounds comprising about 12-20 nucleobases." Further, nowhere in the disclosure of 60/446,374 are there specific lengths of 13, 14, 15, 16, 17, 18, 19, 20, or 21 nucleotides, which are recited in claim 15. Hence, the compound of claim 97 is not adequately supported by the disclosure of 60/446,374.

Further, the disclosure of 60/446,374 is silent about the various, specific chemotherapeutic compounds claimed in claim 50. Moreover, the alleged *in vivo* working examples described in 60/446,374 do not provide any results; they are just descriptive experimental protocols. As such, the disclosure of 60/446,374 does not provide adequate enablement for the pharmaceutical compositions claimed in claims 48-50 and 53-54.

Accordingly, the benefit of an earlier filing date for claims 2, 4-9, 14-16, 47-50, 53-54, 91, and 93-105 (some claims by virtue of claim dependency) is denied, and the instant filing date of February 10, 2004 will be the effective filing date for the claimed invention in the instant case.

If applicant believes that the disclosure of 60/446,374 provides adequate support and enablement for the instantly claimed invention in claims 2, 4-9, 14-16, 47-50, 53-54, 91, and 93-105, applicant is advised to point out the particulars (e.g., page numbers) in response to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4-9, 14-16, 47-50, 53-54, 91, and 93-105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Currently, all dependent claims in the instant case depend either directly or indirectly from claim 91, which was newly added in the amendment dated March 21, 2006. Claim 91, as stated above, recites a compound consisting of a total of 12-50 nucleotides. Further, claim 97 recites a compound consisting of a total of 12-20 nucleotides. However, in the instant specification filed on February 10, 2004, nowhere is there adequate support for the specific, closed length limitation of 12-50 nucleotides or 12-20 nucleotides. The specification instead discloses a compound consisting of a total of 8-50 nucleotides (see page 5), or a compound comprising from about 8 to about 60 nucleobases/nucleosides (see page 20), or a compound comprising from about 12 to about 30 nucleobases (see page 20), or a compound comprising about 12-20 nucleobases (see page 20). In the Remarks filed with the claim amendment, applicant states, "No new matter has been added". In so doing, applicant has not pointed out any passage in support of the newly introduced subject matter. As stated above, the instant

specification does not provide a written description for the length parameter of "consisting of a total of 12-50 nucleotides" or "consisting of a total of 12-20 nucleotides". Since applicant has not pointed out where newly introduced claims are supported in actuality, nor does there appear to be a written description of the claim limitations of "consisting of a total of 12-50" and "consisting of a total of 12-20" in the application as filed. Accordingly, the specification does not convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed, and the claims as amended introduce new matter, which was not described in the application as originally filed.

Claim 50 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 50 is recites myriad species of chemotherapeutic compounds, none of which appears to be described in the specification originally filed on February 10, 2004. Furthermore, the specification does not comply with the written description requirement since it is silent about the species claimed in claim 50. In light of the above, the instant specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors conceived of and invented pharmaceutical compositions comprising each of the chemotherapeutic compound species claimed in the instant case. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), which clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (see page 1117). Since the instant specification does not disclose every single species recited in claim 50, it is concluded that the specification does not reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the instant application was filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al. (US 6,566,514 B1, citation of record) in view of Kurreck et al. (*Nucleic Acids Research,* 2002, 30:1911-1918, applicant's citation) and Taylor et al. (US 6,140,125).

The claims are drawn to antisense compounds comprising or consisting of the nucleic acid sequence of "CAAGgaatatcaCGTT" which modulates the expression of thioredoxin, wherein the capitalized letters represent LNA and the non-capitalized letters represent a DNA sugar, wherein the compounds further comprise a pharmaceutically acceptable carrier or a chemotherapeutic agent or an anti-inflammatory agent.

Wright et al. teach that antisense oligonucleotides that are complementary to the thioredoxin gene can be readily designed by utilizing commercially available computer programs and databases, such as OLIGO Primer Analysis Software, Version 5.0 and the BLASTN program of the University of Wisconsin Computer group (GCG) software with the NCBI databases. See columns 8-9. They teach antisense compounds comprising an anti-thioredoxin antisense oligonucleotide of about 17 to about 50 (or about 20 to about 50) nucleotides in length and a pharmaceutically acceptable carrier. See columns 4-5. They teach that the state of the art pertaining to thioredoxin is such that thioredoxin has been reported to be overexpressed in some primary tumors and induce increased tumor growth and that it has been known to reduce sensitivity to a variety of anticancer drugs. See columns 3-4. They teach that antisense compounds directed against thioredoxin therefore are promising therapeutic compounds for the treatment of cancer. See column 4, lines 16-21. In fact, Wright et al. show that antisense compounds against thioredoxin inhibit human tumor cell growth in mice *in vivo*. See Example 5. They further teach that the anti-thioredoxin antisense compound further comprises a chemotherapeutic agent, wherein the antisense oligonucleotide is chimeric oligonucleotide containing two or more chemically distinct regions wherein the chemically modified nucleotides confer beneficial properties such as increased resistance and cellular uptake. See columns 5 and

7. They also teach antisense compounds comprising an anti-thioredoxin antisense oligonucleotide in conjunction with a chemotherapeutic agent such as 5-FU. See column 19. Wright et al. do not teach antisense compounds comprising or consisting of the nucleic acid sequence of "CAAGGAATATCACGTT", and neither do they teach a chimeric structure comprising beta-D-oxy-LNA.

Kurreck et al. teach methods of designing and making optimal chimeric antisense oligonucleotides containing LNAs, which are more stable and specific *in vivo* than those containing phosphorothioates or 2'-O-methyls. They teach that the most efficient and stable antisense oligonucleotides are designed such that three or four LNAs flank a stretch of seven or eight DNA monomers. They teach that the stretch of seven or eight DNA monomers are necessary for activation of RNase H activation for target mRNA cleavage, which is greatly aided by the flanking LNAs that accelerate the target mRNA cleavage. They teach that their *in vivo* data show that chimeric LNA/DNA oligonucleotides are promising new antisense agents. See the entire reference.

Taylor et al. teach that antisense compounds comprise one or more chemotherapeutic agents such as doxorubicin, bleomycin, and 5-FU or anti-inflammatory or antiviral agents such as corticosteroids, ribivirin, and ganciclovir. They further teach that the antisense compounds can be designed as prodrugs. See columns 10 and 24. They teach that preferred target sites for an antisense compound are located within the coding region of the target gene. It is noted that the presently claimed target site is located within exon 3 of the human thioredoxin gene that comprises a total of 5 exons. They teach that once one or more target sites have been identified,

chimeric antisense compounds can be designed and produced conveniently and routinely through the well-known technique of solid phase synthesis. See columns 3-4 and 9-10.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to arrive at the instantly claimed invention by combining the teachings of the cited prior art references.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success primarily because antisense compounds comprising antisense oligonucleotides targeted to the human thioredoxin gene and a pharmaceutically acceptable carrier, which not only modulate thioredoxin gene expression *in vivo* but also reduce tumor cell growth *in vivo* were known in the art as taught by Wrights et al. As such, the potential clinical or therapeutic utility of anti-thioredoxin antisense compounds was clearly known in the art before the claimed invention was made. Further, Wright et al. expressly taught the desirability of making chimeric antisense compounds that confer increased resistance and stability. As detailed above, use of chimeric antisense compounds was routine and commonplace in the art as evidenced by the teachings of Kurreck et al. and Taylor et al. Further, the particular antisense oligonucleotide design comprising a stretch of seven to eight DNA monomers flanked by two distinct LNA regions as claimed in the instant case was known to be the most stable and effective chimeric antisense oligonucleotide as taught by Kurreck et al. In sum, the LNA/DNA chimeric antisense oligonucleotides targeted to the human thioredoxin gene would have been *prima facie* obvious at the time of the invention. Moreover, both Wright et al. and Taylor et al. taught that antisense oligonucleotides are conveniently and routinely designed and made by using commercially available computer programs and techniques. Further, Taylor et al. taught

that one of the preferred target sites for antisense oligonucleotides are located within coding regions such as exons. The presently claimed target gene is a relatively small gene comprising 5 exons and the instantly claimed target sequence is found to be located within exon 3. To further elaborate, the coding region of the human thioredoxin gene consists of 318 nucleotides in length starting from the ATG start codon and ending with the TAA termination codon. As such, selecting preferred target sites and identifying an optimal one would have been no more than a routine screening process for the instantly claimed target gene of a relatively small size. Since targeting exons of a target gene was common knowledge in the art as taught by Taylor et al., and since identifying optimal antisense target sites via computer modeling programs was a known technique in the art as taught by Wright et al., one of ordinary skill in the art knowledgeable of the teachings of Taylor et al. and Wright et al. would have had a reasonable expectation of success in arriving at the claimed antisense compounds wherein the oligonucleotide is targeted to the nucleic acid sequence of "CAAGGAATATCACGTT". Further, antisense compounds further comprising a chemotherapeutic or anti-inflammatory or antiviral agent and making the antisense compounds as prodrugs were known in the art as taught by Wright et al. and Taylor et al. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner